UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,691	12/11/2003	Mikeljon Nikolich	Army176	9351

7590 10/19/2007

U.S. Army Medical Research and Materiel Command
504 Scott Street
Fort Detrick, MD 21702-5012

EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	**PAPER NUMBER**
1645	

MAIL DATE	DELIVERY MODE
10/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,691	NIKOLICH ET AL.	
	Examiner	Art Unit	
	Mark Navarro	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,9,11-15,18-21,23,25-29,32,33,35-40,43-47,49,52-56,58 and 69-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-5,8,9,11-15,18-21,23,25-29,32,33,35-40,43-47,49,52-56,58 and 69-77.

DETAILED ACTION

Applicants amendment filed July 23, 20007 as well as supplemental response filed August 2, 2007 have been received and entered. Claims 6-7, 10, 16-17, 22, 24, 30-31, 34, 41-42, 48, 50-51, 57, and 59-68, and new claims 70-77 have been added. Accordingly, claims 1-5, 8-9, 11-15, 18-21, 23, 25-29, 32-33, 35-40, 43-47, 49, 52-56, 58 and 69-77 are pending in the instant application.

Claim Objections

1. The objection of claims 1, 30 and 41 for not ending with the punctuation mark of a period is withdrawn in view of Applicants amendment.

2. The objection of claims 35, 45-46, 49, and 55-56 for lacking antecedent basis for the term "the immunogenic composition" is withdrawn in view of Applicants amendment.

Claim Rejections - 35 USC § 112

3. The rejection of claims 1-58 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, a written description rejection is withdrawn in view of Applicants amendment.

4. The rejection of claims 36-40, 43-44, and 47under 35 U.S.C. 112, first paragraph,

because the specification, while being enabling for immunogenic compositions, does not reasonably provide enablement for vaccine compositions is maintained.

Additionally in view of Applicants amendment this rejection is applied to claims 45-46, 49, and 76-77.

Applicants are asserting that page 18-page 24 of the specification provides detailed explanation of the vaccine embodiment of the invention. A prototype was developed of a live, attenuated B. melitensis vaccine strain that expresses protective antigens from three known threat agents, and it was tested for safety, immunogenicity and protective efficacy in appropriate animal models. Applicants further assert that description of how to insert heterologous antigens is discussed.

Applicants arguments have been fully considered but are not found to be fully persuasive.

First, Applicants are asserting that page 18-page 24 of the specification provides detailed explanation of the vaccine embodiment of the invention. However, page 19 of Applicants specification sets forth that "use of this plasmid strategy would allow rapid development of a vaccine stably expressing the heterologous antigen." Simply stated, rapid development of a vaccine is not an enabling disclosure for a claim to a vaccine. "If the disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while application is pending, by later publications which add to knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention; sufficiency under first paragraph of 35 USC 112 must be judged as of the filing date." See ***In re Glass*** 181 USPQ 31 (CCPA 1974).

Second, Applicants assert that a prototype was developed of a live, attenuated B. melitensis vaccine strain that expresses protective antigens from three known threat agents, and it was tested for safety, immunogenicity and protective efficacy in appropriate animal models. However, Applicants are respectfully directed back to the claims. The claims encompass vaccines for "non-brucellosis disease." More specifically, the vaccine encompasses P. falsiparum antigens as the vaccine component. Applicants have completely ignored the teachings of Druilhe et al and Hoffman et al which teach that "An effective vaccine against P. falciparum malaria remains one of the great challenges of medicine." Applicants specification simply does not solve the problem of how to overcome one of the great challenges of medicine.

Finally, Applicants assert that description of how to insert heterologous antigens is discussed. However, as set forth above, a vaccine to P. falciparum is far more complex than simply describing how to insert heterolgous antigens. This concept has been well known for decades, yet P. falciparum still remains without a vaccine.

Facts that should be considered in determining whether a specification is enabling, or if it would require an undue amount of experimentation to practice the invention include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. See In re Wands, 858 F.2d 731,737, 8 USPQ2d

1400, 1403 (Fed. Cir. 1988). The Federal Circuit has noted, however, that only those factors that are relevant based on the facts need to be addressed. See Enzo Biochem. Inc. v. Calgene, Inc. 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed. Cir 1999).

First, Druilhe et al (US Publication 2005/0266017) sets forth that in the search for a vaccine against the agent responsible for malaria, "biologists are confronted with various problems not observed with other infectious agents such as viruses or bacteria." Some of the specific difficulties disclosed by Druilhe et al include: the antigenic diversity of the parasite, studies show that more than 50% of the known antigens exhibit a high degree of polymorphism from one strain to another, the host parasite relationship is very subtle, for a given parasite it is very different depending on the host in which it evolves, this leads to the difficulty of interpretation of the results obtained in the experimental models. (See paragraphs 9-12).

Second, Hoffman et al (US Publication 2005/0208078) set forth that "the process of developing an effective, sustainable vaccine against infections like P. falciparum have proven to be slower, more difficult and complex than expected." Hoffman et al further set forth that "An effective vaccine against P. falciparum malaria remains one of the great challenges of medicine. (See paragraph 5).

A vaccine "must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough." In re Wright, 999 F.2d 1557,1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Given the lack of guidance, lack of working examples, and the unpredictable nature of the invention, one of skill in the art would be forced into excessive

experimentation in order to practice the instantly claimed invention.

Applicants are strongly cautioned that while only one member of the Markush recited in claim 44 (malaria antigens) has been addressed, it is not a sign that the remaining members would be deemed enabled as vaccine compositions.

For reasons of record this rejection is maintained.

5. The rejection of claims 4-7, 14-17, 28-31, 39-42, and 69 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of Applicants response.

Claim Rejections - 35 USC § 102

6. The rejection of claims 52-58 under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nikolich et al is maintained.

Applicants have asserted that the claims have been amended to distinguish over the prior art by reciting: the Brucella contains at least two mutations so as to effect sufficient attenuation, the complementation DNA encodes a peptide required for lippolysaccharide O-sidechain synthesis and the association between the Brucella host cell and the DNA construct is such that following exposure to a mammal the DNA

construct gradually separates from the Brucella host cell, where upon the Brucella host cell reverts to a rough phenotype.

Applicants arguments have been fully considered but are not found to be persuasive.

Applicants arguments are persuasive towards claims which require a host cell having "at least two mutations and a complementation DNA fragment which encodes a peptide required for LPS O-sidechain synthesis." However, Claim 52 does not require a host cell having a double mutation. The only elements recited in claim 52 are the DNA construct having a promoter recognizable by Brucella, encoding a heterologous antigen, and a complementation DNA fragment which encodes a peptide required for LPS O-sidechain synthesis. Nikolich et al disclose of complementation DNA fragments which encode a peptide required for LPS O-sidechain synthesis, the preferred embodiment being the wboA gene. Nikolich et al further disclose of providing a means to express antigens of interest as potential therapeuctic or vaccines for human and veterinary use. Combined these two statements result in a recombinant DNA construct having all the elements recited in the claims.

The claims are directed to a recombinant DNA construct replicable in Brucella, which DNA construct comprises: (i) a DNA fragment operably linked to a first promoter recognizable by Brucella and encoding a heterologous antigen and (ii) a complementation DNA fragment which encodes a peptide required for lipopolysaccharide O-sidechain synthesis so as to effect lipopolysaccharide O-sidechain

synthesis in vivo and which is operably linked to the promoter and which complements a rough-conferring mutation in the host cell, thereby effecting a smooth phenotype in the host cell.

Nikolich et al (US Patent Number 6,444,445) disclose of introducing a deletion in the rfbU gene of a strain of Brucella which results in a rough phenotype. (See abstract). Nikolich et al further disclose that when deletion mutant WRR51 was introduced a plasmid containing a synthetic copy of the rfbU gene, the strain became smooth. (See column 2).

As set forth in Applicants specification, rfbU is also referred to as wboA. (See pages 1-2).

It is noted that Nikolich et al did not express any heterologous proteins for generating an immune response. However, Nikolich et al specifically contemplate a means to express antigen of interest as therapeutics or vaccines for human and vetinary use. (See column 4). Accordingly, it would have been prima facie obvious to have chosen a heterologous antigen against which an immune response would be desirable.

For reason of record, this rejection is maintained.

7. The rejection of claims 52-58 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nikolich et al is maintained.

Applicants arguments are identical to those recited above in paragraph number 6, and have been fully addressed in paragraph six above.

Nikolich et al (US Patent Number 6,444,445) disclose of introducing a deletion in the rfbU gene of a strain of Brucella which results in a rough phenotype. (See abstract). Nikolich et al further disclose that when deletion mutant WRR51 was introduced a plasmid containing a synthetic copy of the rfbU gene, the strain became smooth. (See column 2).

As set forth in Applicants specification, rfbU is also referred to as wboA. (See pages 1-2).

It is noted that Nikolich et al did not express any heterologous proteins for generating an immune response. However, Nikolich et al specifically contemplate a means to express antigen of interest as therapeutics or vaccines for human and vetinary use. (See column 4). Accordingly, it would have been prima facie obvious to have chosen a heterologous antigen against which an immune response would be desirable.

8. The rejection of claims 52-58 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nikolich et al is maintained.

Applicants arguments are identical to those recited above in paragraph number 6, and have been fully addressed in paragraph six above.

Nikolich et al (WO 99/37783) disclose of introducing a deletion in the rfbU gene of a strain of Brucella which results in a rough phenotype. (See abstract). Nikolich et al further disclose that when deletion mutant WRR51 was introduced a plasmid containing a synthetic copy of the rfbU gene, the strain became smooth. (See pages 5 and 26).

As set forth in Applicants specification, rfbU is also referred to as wboA. (See pages 1-2).

It is noted that Nikolich et al did not express any heterologous proteins for generating an immune response. However, Nikolich et al specifically contemplate a means to express antigen of interest as therapeutics or vaccines for human and vetinary use, and specifically recite malaria antigens. (See pages 22-23). Accordingly, it would have been prima facie obvious to have chosen a heterologous antigen for expression against which an immune response would be desirable.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. The rejection of Claims 1-58 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,444,445 is maintained.

Additionally this rejection is applied to newly added claims 70-77.

Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims encompasses recombinant DNA constructs replicable in Brucella which complement a rough-conferring mutation in the host cell, thereby effecting a smooth phenotype in the host cell.

Applicants have requested that this rejection be held in abeyance, however, until a terminal disclaimer is made of record, this rejection is maintained for reasons of record.

10. The objection of claims 25-49 under 37 CFR 1.75 as being a substantial duplicate of claims 1-24 is withdrawn.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro whose telephone number is (571) 272-0861. The examiner can normally be reached on 5/4/9.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Navarro
Primary Examiner
October 11, 2007